PEPTIDOMIMETIC INHIBITORS OF THE PEPTIDYL-PROLYL CIS/TRANS ISOMERASE (PIN1)

RELATED APPLICATION

[0001] This application is a national stage application, filed under 35 U.S.C. § 371, of International Application No. PCT/US2019/036938, filed Jun. 13, 2019, which claims the benefit of priority under 35 U.S.C. § 119(e) to U.S. Provisional Application No. 62/685,110, filed on Jun. 14, 2018, each of which is incorporated herein by reference in its entirety.

GOVERNMENT LICENSE RIGHTS

[0002] This invention was made with government support under grant number R01 CA205153 awarded by the National Institutes of Health, grant number R01 CA167677 awarded by the National Institutes of Health, grant number F31 CA225066-02 awarded by the National Institutes of Health, grant number 5 T32 GM007306-41 awarded by the National Institutes of Health, and grant number 5 T32 GM095450-04 awarded by the National Institutes of Health. The government has certain rights in the invention.

BACKGROUND OF THE INVENTION

[0003] Proline is unique among the amino acids because it populates both the cis and trans conformations, providing a backbone conformational switch that is controlled by prolyl isomerization. Due to the high energy barrier associated with cis to trans conversion (25-30 kcal/mol), the intrinsic isomerization process is slow (several minutes) relative to biochemical processes, and therefore catalysis by peptidyl prolyl isomerases (PPIases) is required for efficient isomerization.

[0004] Proline (Pro)-directed serine/threonine (Ser/Thr) phosphorylation (pSer/Thr-Pro) serves an essential role in cell signaling networks and is often dysregulated in cancer. Numerous oncogenes and tumor suppressors are regulated by Pro-directed phosphorylation and/or are part of signaling pathways involving such phosphorylation.

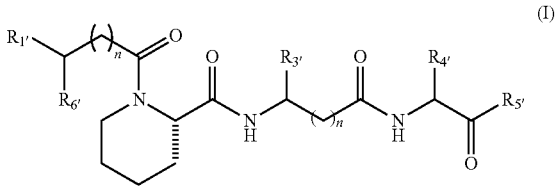
[0005] pSer/Thr-Pro reduces the intrinsically slow cis-trans isomerization process, and also renders the peptide bonds inaccessible for all known peptidyl-prolyl cis-trans isomerases (PPIases), except for peptidyl-prolyl cis-trans isomerase NIMA-interacting 1 (Pin1) and its homologues. Pin1 contains an N-terminal WW domain, which functions as a phosphorylated Ser/Thr-Pro binding module, and a PPIase domain, which catalyzes the cis-trans isomerization. (Zhou et al., Cell. Mol. Life Sci. 56: 788-806 (1999)).

[0006] Pin1-catalysed prolyl isomerization regulates the functions of its substrates through multiple different mechanisms, including controlling catalytic activity, turnover, phosphorylation, interactions with DNA, RNA or other proteins, and subcellular localization and processing. Pin1 often functions as a molecular timer that synchronously controls the amplitude and duration of a given cellular process. Pin1 is tightly regulated normally and its deregulation can have a major impact on the development and treatment of cancer and neurodegenerative diseases, such as Alzheimer disease. (Lu and Zhou, Nat. Rev. Mol. Cell Biol. 5:904-16 (2007)).

[0007] Pin1 is widely overexpressed and/or overactivated in cancers which correlate with poor clinical prognosis. (Lu and Hunter, Cell Res. 24:1033-49 (2014)). It has also been shown that Pin1 single nucleotide polymorphisms (SNPs) that reduce Pin1 expression are associated with a reduced risk for multiple cancers, and that Pin1-null mice are highly resistant to tumorigenesis, even after the overexpression of oncogenes or after the mutation or ablation of tumor suppressors. (Li et al., *PLoS ONE* 8:&88148 (2004); Wulf et al., EMBO J. 23:3397-3407 (2004); Girardini et al., Cancer Cell 20:79-91 (2011); Takahashi et al., Oncogene 26:3835-45 (2007)). Further, Pin1-null mice have been shown to develop normally to adulthood with few defects. (Lee et al., Expert Rev. Mol. Med. 73:e21 (2011)). Further, Pin1 overexpression disrupts cell cycle coordination and leads to chromosome instability and tumorigenesis. Pin1 activates and inactivates more than 40 oncogenes and 20 tumor suppressors, respectively. Many of these Pin1 substrates have a role in self-renewal, replicative potential and frequency of cancer stem cells (CSCs). (Zhou and Lu, Nat. Rev. Cancer 16: 463-78 (2016)). Therefore, Pin1 inhibitors may have the desirable ability to simultaneously block multiple cancer-driving pathways and CSC expansion and differentiation with limited toxicity.

SUMMARY OF THE INVENTION

[0008] A first aspect of the present invention is directed to a compound having a structure as represented by formula (I):



(I)

wherein each n is independently 0 or 1;

R_1' is a phosphorylated alkyl, a hydroxyalkyl, a sulfone, an optionally substituted aralkyl, a carboxylic acid or an ester;

$R_{3'}$ is an optionally substituted aralkyl, a ketone or an optionally substituted heteroaralkyl;

$R_{4'}$ is an alkyl urea, an alkyl guanidine, a hydroxyalkyl, an amide, an optionally substituted heteroaralkyl or an optionally substituted aralkyl; and

$R_{5'}$ is an optionally substituted N-aralkyl, an alkoxy, an optionally substituted N-methyl-aralkyl, an optionally substituted N-methyl-aryl, an optionally substituted N-aryl, an optionally substituted N-cyclyl, an optionally substituted heterocyclyl or an N-alkyl; and

$R_{6'}$ is a sulfonamide or an amide; or a pharmaceutically acceptable salt or stereoisomer thereof, wherein the compound is cell permeable and binds Pin1 with a Ki of less than 1 μM.

[0009] In some embodiments, R_1' is a phosphorylated alkyl, a hydroxyalkyl, a sulfone, an optionally substituted aralkyl, a carboxylic acid or an ester except for